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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,724	09/08/1999	GERLINDE LENZEN	045636-5025	3497

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/319,724	LENZEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *22,23,25,26 and 28-48* is/are pending in the application.

4a) Of the above claim(s) *30-32,38 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *22,25,28,29,33-37,39,47 and 48* is/are rejected.

7)☐ Claim(s) *23 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 7/24/03, have been entered in full.

Claims 30-32, 38, 40-46 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously.

Applicant is notified that any outstanding rejection or objection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and/or Applicant's persuasive arguments.

Drawings

New corrected drawings are required in this application because, unfortunately, the drawings filed by Applicant on 7/23/03 have become separated from the file and were not scanned into the database. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Response to Amendment

Claims 22, 25, 29, 33, 34, 36, 37, 47 and 48 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding a protein of SEQ ID NO: 14 and the portion thereof capable of binding ICYP i.e. SEQ ID NO: 1,

does not reasonably provide enablement for polynucleotides that do not encode a polypeptide of SEQ ID NO: 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, as set forth previously and reiterated below.

The specification asserts that a polypeptides of SEQ ID NO: 1 and 14 are capable of binding ICYP and are thus useful in the study of ICYP transduction and drug development, yet the claims claim a vast genus of polynucleotides that do not encode either SEQ ID NO: 1 or 14. The claims encompass polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 14, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 14. Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 14, but which still retain a desired property of the polypeptide of SEQ ID NO: 14. The claims require polypeptides comprising only portions of SEQ ID NO: 14, e.g. those comprising the formula sequence recited in claim 22 or polynucleotides that may only hybridize to polynucleotide encoding of SEQ ID NO: 14 or to only a portion of such a polynucleotide, e.g. claims 47 and 48. Thus, the vast majority of encoded polypeptides are amino acid sequence variants of SEQ ID NO: 14, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 14, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 14 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in

structure or difference in function between the protein corresponding to SEQ ID NO: 14 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 14 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 14, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 14. Conversely, if a protein variant of SEQ ID NO: 14 need not have a disclosed property, the specification has failed to teach how to use such a variant. The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 14 nor sufficient guidance so as to enable one of skill in the art to make such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of

changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 14 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The specification has also failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 14, e.g. no disorder or phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might now where to obtain a variant. The

specification merely offers the skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations.

Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that the claims encompass natural species variants and that the skilled artisan could readily isolate proteins from other species that meet the claim limitations. This argument has been fully considered but not deemed persuasive. First, it should be pointed out that the claims are essentially infinitely more broad than a claim that was limited to natural species variants – of which there is no currently pending claim. Importantly, however, the mere invitation to try the experiments discussed in example 3 with other species does not constitute an enabling disclosure for polypeptides that need only have the 15 or 16 amino acids recited in SEQ ID NO: 5 and 6. Further it does not appear that any of the clones uncovered in the BLAST searches, discussed by Applicant in the response and also in the Declaration of Toshinari Sugasawa, were available at the time of filing of the instant application. So, it appears that Applicant is suggesting that the specification enables an artisan to find species variants by inviting him to wait for someone else to clone them and then use the instantly disclosed

sequences to find them in a database The artisan would not consider that to be adequate teaching.

Claims 22, 25, 29, 33, 34, 36, 37, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and reiterated below:

The specification discloses a polynucleotide of SEQ ID NO: 13, yet the claims encompass polynucleotides not described in the specification, i.e. polynucleotides which comprise only portions of SEQ ID NO: 13, e.g. sequences from other species, mutated sequences, allelic variants, or sequences that might hybridize to a portion of SEQ ID NO: 13. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 1, and a single portion thereof SEQ ID NO: 2, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs,

defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 13, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

Thus, with the exception of the of the polynucleotide of SEQ ID NO: 1 and 13, and other polynucleotides which encode a polypeptide of SEQ ID NO: 14, the skilled artisan cannot envision encompassed variants. Therefore, only polynucleotides encoding a polypeptide of SEQ ID NO: 14, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant argues that Lilly is only relevant to the particular circumstances of that case which happened at time when biotechnology was much less developed than it is now. Applicant is referred to a recent decision by the U.S. Court of Appeals for the Federal Circuit, *Noelle v. Lederman et al.*, Interference No. 104,415, decided January 20, 2004, wherein the fact pattern closely resembles the instant fact pattern. While the claims in that case were directed to antibodies, the decision was based on whether or not Appellant (*Noelle*) was in possession of the protein that the antibodies would be raised against. *Noelle* had described the murine protein and an antibody, but the claims were to a human antibody that bound to the human homolog of the murine protein. The court stated that if *Noelle* was in possession of the human protein, then antibodies to the human protein would be adequately described. However, the court determined that simply disclosing the murine protein did not put *Noelle* in possession of the human protein.

There is no reason to think that the court would have found that *Noelle* was in possession of the of other species variants if *Noelle* had simply described the human protein, as in the instant case. To the contrary, the court agreed with the definition of the written description requirement as set forth in *Vas-Cath*, 935 F.2d at 1563-64, and quoting *Fiers v. Revel* 984 F.2d 1164, 1170 (Fed. Cir. 1993), that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

Applicant further argues that the claims have been adequately described by the recitation structural requirements, e.g. SEQ ID NO: 5 and 6, and functional characteristics. This argument has been fully considered but not deemed persuasive. Regarding the structural characteristics, the disclosure of SEQ ID NO: 5 and 6 would constitute less than 3% of a protein expected to have the required functional properties, e.g. SEQ ID NO: 14 is 576 amino acids in length. Thus, greater than 97% of the claimed proteins have not been described. Further, the skilled artisan appreciates that simply verbalizing or writing down that a protein should have certain functional properties in no way places one in possession of such a protein.

Conclusion

Claims 23 and 26 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

4/2/04

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